SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

BRUKINSA® (80 mg, capsules)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each capsule contains 80 mg zanubrutinib.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Size 0, white to off-white, opaque hard capsule imprinted with black “ZANU 80” printing on cap, which contains white to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BRUKINSA (zanubrutinib) is indicated:

- For the treatment of adult patients with Waldenström’s macroglobulinaemia (WM).
- For the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.
- For the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy.
- For the treatment of adult patients with chronic lymphocytic leukemia /small lymphocytic lymphoma (CLL/SLL).

4.2 Posology and method of administration

Posology

The recommended total daily oral dose of BRUKINSA is 320 mg. BRUKINSA may be taken as either 320 mg (four 80 mg capsules) once daily or 160 mg (two 80 mg capsules) twice daily.

Treatment with BRUKINSA should continue until disease progression or unacceptable toxicity.

Dosage Adjustment

Recommended dose modifications of BRUKINSA for Grade ≥ 3 adverse reactions are provided in Table 1.

Table 1: Recommended Dose Modification for Adverse Reaction

Event	**Adverse Reaction Occurrence**	**Dose Modification (Starting Dose: 160 mg twice daily)**
≥ Grade 3 non-haematological toxicities Grade 3 febrile neutropenia	First	Interrupt BRUKINSA Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 160 mg twice daily or 320 mg once daily
Grade 3 thrombocytopenia with significant bleeding	Second	Interrupt BRUKINSA Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 80 mg twice daily or 160 mg once daily

Event	**Adverse Reaction Occurrence**	**Dose Modification (Starting Dose: 160 mg twice daily)**
Grade 4 neutropenia (lasting > 10 consecutive days) Grade 4 thrombocytopenia (lasting > 10 consecutive days)	Third	Interrupt BRUKINSA Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 80 mg once daily
	Fourth	Discontinue BRUKINSA

Asymptomatic lymphocytosis should not be regarded as an adverse reaction, and these patients should continue taking zanubrutinib.

Recommended dose modification for use with CYP3A inhibitors or inducers are provided in Table 2.

Table 2: Use with CYP3A Inhibitors or Inducers

CYP3A	**Co-administered Drug**	**Recommended Dose**
Inhibition	Strong CYP3A inhibitor	80 mg once daily Interrupt dose as recommended for adverse reactions
	Moderate CYP3A inhibitor	80 mg twice daily Modify dose as recommended for adverse reactions
Induction	Strong CYP3A inducer	Avoid concomitant use; Consider alternative agents with less CYP3A induction
	Moderate CYP3A inducer	Use with caution.

After discontinuation of a CYP3A inhibitor, resume previous dose of BRUKINSA.

Special populations

Elderly population:

Of the 847 patients in clinical trials of BRUKINSA, 53 % were 65 years of age or older, and 20 % were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and those younger than 65 years.

No dose modification is necessary based on age.

Renal impairment:

No dosage modification is recommended in patients with mild to moderate renal impairment (CrCl ≥ 30 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients with severe renal impairment (CrCl < 30 mL/min) or on dialysis.

Hepatic impairment:

No dose modification is recommended in patients with mild or moderate hepatic impairment. The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. Monitor closely for adverse reactions of BRUKINSA in patients with hepatic impairment.

Paediatric population

The safety and efficacy of BRUKINSA in children and adolescents aged less than 18 years have not been established, therefore BRUKINSA is not recommended for use in children under the age of 18 years.

Method of administration

For oral use.

BRUKINSA capsules should be swallowed whole with water, BRUKINSA can be taken with or without food. The capsule should not be chewed, dissolved, or opened. BRUKINSA must not be taken with grapefruit juice, grapefruit and /or Seville oranges.

4.3 Contraindications

Hypersensitivity to the active substance, zanubrutinib or to any of the excipients.

4.4 Special warnings and precautions for use

Treatment with BRUKINSA should be initiated and supervised by a qualified doctor experienced in the use of anticancer therapies.

Carcinogenesis and Mutagenesis

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma have occurred in 12,4 % patients with hematological malignancies treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma, squamous cell carcinoma of skin), reported in 7,4 % of patients. Monitor patients for skin cancer and advise patients to use sun protection.

Cardiovascular

Patients with active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia, class 3 or 4 congestive heart failure or recent myocardial infarction, were excluded from clinical trials of BRUKINSA.

Atrial Fibrillation and Flutter

Atrial fibrillation and atrial flutter have occurred in 3,2 % of patients with haematological malignancies treated with BRUKINSA monotherapy. This risk may be increased in patients with cardiac risk factors, hypertension, and acute infections. Grade 3 and above events were

reported in 1,4 % of patients. Monitor for signs and symptoms of atrial fibrillation and atrial flutter and manage as appropriate.

Haematologic

Cytopenias

Grade 3 or 4 neutropenia (18,5 %, including febrile neutropenia, thrombocytopenia (5,7 % and anaemia (5,2 %) based on laboratory measurements were reported in patients with hematologic malignancies treated with BRUKINSA monotherapy (see section 4.8). Monitor complete blood counts regularly during treatment (see Monitoring and Laboratory Tests). Reduce dose, interrupt or discontinue treatment as necessary (See section 4.2) and treat using growth factors or transfusion as necessary.

Immune

Infections

Serious and fatal infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with haematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred 21,8 % of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) or varicella zoster reactivation (herpes zoster) have occurred.

Monitor patients for signs and symptoms of infection and treat appropriately. Consider prophylaxis according to standard of care in patients who are at increased risk for infections

Endocrine and Metabolism

Tumour Lysis Syndrome

Tumour lysis syndrome has been infrequently reported with BRUKINSA therapy, particularly in patients who were treated for CLL/SLL. Assess the baseline risk (e.g., high tumour

burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Monitoring and Laboratory Tests

- Monitor complete blood counts as per routine clinical practice.
- Monitor for symptoms (e.g., palpitations, dizziness, syncope, chest pain, dyspnoea) of atrial fibrillation and atrial flutter and obtain an echocardiogram (ECG) as appropriate.
- Monitor patients for the appearance of skin cancers.
- Monitor patients for signs and symptoms of infection and treat as medically appropriate.
- Monitor patients for signs of bleeding.

Peri-Operative Considerations

Patients with major surgery within 4 weeks of the first dose of study drug were excluded from clinical trials with BRUKINSA. Consider the benefit-risk of withholding BRUKINSA for 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Respiratory

Interstitial Lung Disease (ILD)

Cases of suspected ILD have occurred in 0,6 % of patients with haematological malignancies treated with BRUKINSA monotherapy. However, none were confirmed by biopsy. Monitor patients for signs and symptoms of ILD. Advise patients to report promptly any new or worsening respiratory symptoms. If ILD is suspected, interrupt BRUKINSA and treat promptly and appropriately. If ILD is confirmed, discontinue BRUKINSA.

Vascular

Haemorrhage

1.3.1.1 Professional Information

Serious and fatal haemorrhagic events have occurred in patients with haematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal haemorrhage, haematuria and hemothorax have been reported in 3,84 % of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 48,1 % of patients with haematological malignancies treated with BRUKINSA monotherapy.

BRUKINSA may increase the risk of haemorrhage in patients receiving antiplatelet or anticoagulant therapies. Patients were excluded from BRUKINSA studies if they had recent history of stroke or intracranial haemorrhage, or if they required warfarin or other vitamin K antagonists.
Patients should be monitored for signs of bleeding. Bleeding events should be managed with supportive measures, including transfusions, and specialized care as needed. Reduce dose, interrupt or discontinue treatment as necessary (See section 4.2). For any intracranial haemorrhage, treatment should be discontinued.

4.5 Interaction with other medicines and other forms of Interaction

Zanubrutinib is primarily metabolized by CYP3A. Concomitant use of BRUKINSA with medicinal products that strongly or moderately inhibit CYP3A can increase zanubrutinib plasma concentrations, which may increase the risk of BRUKINSA toxicities.

Concomitant use of BRUKINSA with moderate or strong CYP3A inducers can decrease zanubrutinib plasma concentrations, which may reduce BRUKINSA efficacy.

Medicine Interactions

The medicines listed in Table 3 are based on either medicine interaction studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 3: Medicine Interactions

Common Name	Source of Evidence	Effect	Clinical Comment
Active substances that may increase zanubrutinib plasma concentrations			
Strong CYP3A inhibitors (e.g., posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir)	CT	Coadministration of itraconazole (200 mg once daily) increased zanubrutinib C_{max} by 157 % and AUC by 278 %.	Reduce BRUKINSA dosage to 80 mg once daily when co-administered with strong CYP3A inhibitors (see section 4.2)
Moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant)	P	Coadministration of erythromycin (500 mg four time daily) was predicted to increase zanubrutinib C_{max} by 284 % and AUC by 317 %; Coadministration of fluconazole (200 mg once daily) was predicted to increase zanubrutinib C_{max} by 179 % and AUC by 177 %; Coadministration of fluconazole (400 mg once daily) was predicted to increase	Reduce BRUKINSA dosage to 80 mg twice daily when co-administered with moderate CYP3A inhibitors (see section 4.2)

Common Name	Source of Evidence	Effect	Clinical Comment
		zanubrutinib C_{max} by 270 % and AUC by 284 %; Coadministration of diltiazem (200 mg once daily) was predicted to increase zanubrutinib C_{max} by 151 % and AUC by 157 %.	
Active substances that may decrease zanubrutinib plasma concentrations			
Strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin)	CT	Co-administration of rifampin (600 mg once a day for 8 days) decreased zanubrutinib C_{max} by 92 % and AUC by 93 %.	Avoid concomitant use of BRUKINSA with strong CYP3A inducers.
Moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin)	CT	Co-administration of rifabutin (300 mg once a day for 9 days) decreased zanubrutinib C_{max} by 48% and AUC by 44%.	Use with caution Ref: BGB-3111-112

CT = Clinical Trial; P = Predicted

Clinical Studies

Effects of Gastric Acid Reducing Agents on zanubrutinib:

No clinically significant differences in zanubrutinib pharmacokinetics were observed when co-administered with gastric acid reducing agents (proton pump inhibitors, H2-receptor

antagonists).

Effects of zanubrutinib on CYP3A Substrates:

Co-administration of multiple doses of zanubrutinib decreased midazolam (CYP3A substrate) C_{max} by 30 % and AUC by 47 %.

Effects of zanubrutinib on CYP2C19 Substrates:

Co-administration of multiple doses of zanubrutinib decreased omeprazole (CYP2C19 substrate) C_{max} by 20 % and AUC by 36 %.

Effects of zanubrutinib on Other CYP Substrates:

No clinically significant differences were observed with warfarin (CYP2C9 substrate) pharmacokinetics or predicted with rosiglitazone (CYP2C8 substrate) pharmacokinetics when co-administered with zanubrutinib.

Effects of zanubrutinib on Transporter Systems:

Co-administration of multiple doses of zanubrutinib increased digoxin (P-gp substrate) C_{max} by 34 % and AUC by 11 %. No clinically significant differences in the pharmacokinetics of rosuvastatin (BCRP substrate) were observed when co-administered with zanubrutinib.

In Vitro Studies

Effects of zanubrutinib on CYP2B6 Substrates:

In vitro, zanubrutinib is a weak inducer of CYP2B6.

Effects of Transporters on zanubrutinib:

In vitro, zanubrutinib is likely to be a substrate of P-gp. Zanubrutinib is not a substrate or inhibitor of OAT1, OAT3, OCT2, OATP1B1, or OATP1B3.

Medicine-Food Interactions

Avoid concomitant use with grapefruit, grapefruit juice and Seville oranges, as they contain inhibitors of CYP3A and may increase zanubrutinib plasma concentrations.

No clinically significant differences in zanubrutinib AUC or C_{max} were observed following administration of a high-fat meal (approximately 1 000 calories with 50 % of total caloric content from fat) in healthy subjects.

Medicine-Herb Interactions

Avoid St. John's wort which may unpredictably decrease zanubrutinib plasma concentrations.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Women of child-bearing potential must use highly effective contraceptive measures while taking BRUKINSA and at least for one week after stopping treatment. Women who use hormonal methods of birth control must add a barrier method.

Pregnancy

There are no adequate and well-controlled studies of BRUKINSA in pregnant women. Based on findings in animals, zanubrutinib may cause foetal harm when administered to pregnant women (see section 5.3). If BRUKINSA is used during pregnancy or if the patient becomes pregnant while taking BRUKINSA, the patient should be apprised of the potential hazard to the fetus.

Breastfeeding

It is unknown if BRUKINSA is excreted in human milk. Because many medicines are excreted in human milk and because of the potential for serious adverse reactions from BRUKINSA in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for at least two weeks following the last dose.

Fertility

No effect on male or female fertility was noted in rats but morphological abnormalities in sperm and increased post-implantation loss were noted at 300 mg/kg/day (see section 5.3).

4.7 Effects on ability to drive and use machines

No specific studies have been conducted to evaluate the influence of BRUKINSA treatment on the ability to drive or operate heavy machinery. Fatigue, dizziness, and asthenia have been reported in some patients taking BRUKINSA and should be considered when assessing a patient's ability to drive or operate machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile is based on pooled data from 1550 patients with B-cell malignancies treated with BRUKINSA monotherapy in 9 clinical trials, including one Phase 1 clinical study (BGB-3111-1002), one Phase 1/2 clinical study (BGB-3111-AU-003), four Phase 2 studies (BGB-3111-205, BGB-3111-206, and BGB-3111-210, BGB-3111-214), and three Phase 3 clinical studies (BGB-3111-302, BGB -3111-304, BGB-3111-305). Among 1550 patients receiving zanubrutinib, the median duration of exposure was 22,95 months. Among the patients, 73,6 % patients were exposed to zanubrutinib for at least 1 year, 48 % were exposed for at least 2 years, 23,5 % were exposed for at least 3 years and 6,7 % were exposed for at least 4 years.

The most common adverse reactions (≥ 10 % grouped terms) were upper respiratory tract infection, neutropenia, haemorrhage/haematoma, bruising, rash, musculoskeletal pain, diarrhoea, cough, pneumonia, fatigue, thrombocytopenia, anaemia, constipation, and dizziness.

Overall, 17,7 % of patients experienced serious adverse reactions. The most frequently reported serious adverse reactions (≥ 1 %, grouped terms) were pneumonia (9,2 %), haemorrhage /hematoma (2,5 %), neutropenia (1,9 %), and anaemia (1,4 %).

Deaths due to adverse events within 30 days were reported in 1,4 % of patients. The most common treatment-emergent adverse event leading to death (≥ 1 %, grouped term) was pneumonia (1,2 %).

Of the 1550 patients treated with BRUKINSA, 41 (2,6 %) patients discontinued treatment due to adverse reactions. The most frequent adverse reaction leading to treatment discontinuation (≥ 1 %, grouped term) was pneumonia (1,4 %). Adverse reactions leading to dose reduction occurred in 4,6 % of patients. The most frequent adverse reactions leading to dose reduction were neutropenia (0,9 %) and pneumonia (0,8 %).

Tabulated list of adverse reactions

Adverse reactions in patients treated with BRUKINSA for B-cell malignancies are listed below by system organ class and frequency grouping. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to <1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 4: Adverse reactions reported in clinical studies in patients with B-cell malignancies

MedDRA SOC	**MedDRA Terms**	**All Grades* (%)**	**Grade 3 or higher (%)**
Infections and infestations	Upper respiratory tract infection[§]	Very common (33)	2
	Pneumonia[§#]	Very common (18)	9
	Pneumonia	Very common (12)	7
	Lower respiratory tract infection	Common (5)	<1
	Urinary tract infection	Very common (12)	2
	Bronchitis	Common (4)	<1
	Hepatitis B reactivation	Uncommon (<1)	<1

Blood and lymphatic system disorders	Neutropenia[§]	Very common (28)	19
	Febrile neutropenia	Common (1)	1
	Thrombocytopenia[§]	Very common (16)	6
	Anaemia[§]	Very common (14)	5
Nervous system disorder	Dizziness[§]	Very common (11)	<1
Cardiac disorders	Atrial fibrillation and flutter	Common (3)	1
Vascular disorders	Bruising[§]	Very common (30)	<1
	Contusion	Very common (18)	0
	Petechiae	Common (7)	<1
	Purpura	Common (5)	<1
	Ecchymosis	Common (2)	<1
	Haemorrhage/Haematoma[§ #]	Very common (27)	3
	Haematuria	Very common (10)	<1
	Epistaxis	Common (7)	<1
	Gastrointestinal haemorrhage	Uncommon (<1)	<1
	Hypertension[§]	Very common (13)	7
Respiratory, thoracic and mediastinal disorders	Cough	Very common (19)	<1
Gastrointestinal disorders	Diarrhoea	Very common (19)	2
	Constipation	Very common (12)	<1
	Nausea [µ]	Very common (11)	<1

	Vomiting [µ]	Common (6)	<1
Skin and subcutaneous tissue disorders	Rash[§]	Very common (23)	<1
	Pruritus	Common (7)	<1
	Dermatitis exfoliative general	Unknown	Unknown
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[§]	Very common (23)	2
	Arthralgia	Very common (13)	<1
	Back pain	Very common (10)	<1
General disorders and administration site conditions	Fatigue[§]	Very common (16)	1
	Fatigue	Very common (12)	1
	Asthenia	Common (4)	<1
	Oedema peripheral	Common (7)	<1
Metabolism and nutrition disorders	Tumour lysis syndrome[§#]	Uncommon (<1)	<1

Investigations†	Absolute neutrophil count decreased†±	Very common (49)	21
	Platelets decreased†±	Very common (36)	7
	Haemoglobin decreased†±	Very common (23)	4

* Grades were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

† Based on laboratory measurements.

± Percentages are based on number of patients with both baseline and at least one postbaseline assessment available.

§ Includes multiple adverse reaction terms

Includes events with fatal outcome.

µ Treatment-emergent Adverse Events with no established causal relationship with the medicine

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA on the SAHPRA website at: https://medsafety.sahpra.org.za/#download1, via email at: adr@sahpra.org.za or via telephone at: 0125010311

4.9 Overdose

There is no specific treatment for BRUKINSA overdose. For patients who experience overdose closely monitor and provide appropriate supportive treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION: A 26 - Cytostatics

Pharmacotherapeutic group and ATC code: Antineoplastic agents, Bruton's tyrosine kinase inhibitors: L01EL03.

Mechanism of action:

Zanubrutinib is a potent and highly selective small-molecule inhibitor of BTK. Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion.
In nonclinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumor growth.

Pharmacodynamic effects:

BTK occupancy in peripheral blood mononuclear cells and lymph node biopsies

The median steady-state BTK occupancy in peripheral blood mononuclear cells was maintained at 100 % over 24 hours at a total daily dose of 320 mg BRUKINSA in patients with B-cell malignancies. The median steady-state BTK occupancy in lymph nodes was 94 % and 100 % following the approved recommended dosage of 320 mg once daily, or 160 mg twice daily respectively.

Cardiac electrophysiology

At the approved recommended doses (320 mg once daily or 160 mg twice daily), there were no clinically relevant effects on the QTc interval. In a thorough QT study in healthy subjects, a single dose of 160mg or 480 mg zanubrutinib did not prolong the QT interval to any

clinically relevant extent. The maximum plasma exposure of zanubrutinib in this study was close to the maximum plasma exposure observed in patients following the recommended dose of 320 mg once daily.
The effect of BRUKINSA on the QTc interval above the therapeutic exposure has not been evaluated.

Clinical safety and efficacy:

The Treatment Of Adult Patients With Waldenström's Macroglobulinemia (WM)
The safety and efficacy of BRUKINSA were evaluated in a randomized, open-label, multi-center study comparing BRUKINSA and an active control in 201 patients with MYD88 mutated (*MYD88*^{MUT}) WM (BGB-3111-302). In addition, a subset of WM patients found to have *MYD88* wildtype (*MYD88*^{WT}) by gene sequencing (N=26), or whose mutational status was missing or inconclusive (N=2), were enrolled in a third, non-randomised study arm.

The primary outcome measure was rate of Complete Response (CR) or Very Good Partial Response (VGPR), in RR *MYD88*^{MUT} as assessed by Independent Review Committee (IRC) with adaptation of the response criteria updated at the Sixth IWWM. The secondary endpoints for Cohort 1 included major response rate (MRR), duration of response, rate of CR or VGPR assessed by investigator, and progression-free survival (PFS).

The primary efficacy analysis for patients with RR WM with *MYD88* mutation (*MYD88*^{MUT}), Cohort 1, was conducted at a median follow-up of 18,8 months in study BGB-3111-302 (ASPEN). As per IRC assessment, the primary study results failed to reach statistical significance in the RR Analysis Set (2-sided p = 0,12), thus the study did not meet the primary efficacy endpoint. Consequently, all other endpoints are considered descriptive. Efficacy results, as assessed by Investigator, were consistent with the primary efficacy analysis.

MRRs were 78 % (95 % CI: 68, 87) and 80 % (95 % CI: 70, 88) in the BRUKINSA and comparator arms of the primary efficacy set (RR *WM MYD88^{MUT}* patients), respectively. MRRs for treatment naive patients were 74% (95 % CI: 49, 91) and 67 % (95 % CI: 41, 87) in the BRUKINSA and the comparator arms, respectively.

Median DoR of CR or VGPR and PFS were not reached in either arm of the primary efficacy set of RR *MYD88^{MUT}* WM patients.

In the non-randomised exploratory subset of BRUKINSA-treated *MYD88^{WT}* WM patients (Cohort 2), VGPR or CR rates as assessed by IRC were 20 % (95 % CI: 1, 72) for treatment-naïve patients (n=5) and 29 % (95 % CI: 11, 52), for RR patients (n=21). No CRs were observed.

The Treatment Of Adult Patients With Mantle Cell Lymphoma (MCL) Who Have Received At Least One Prior Therapy

The safety and efficacy of BRUKINSA in patients with MCL were evaluated in an open-label, multi-center, single-arm Phase 2 study (BGB-3111-206) of 86 previously treated patients, and an open-label, dose escalation and expansion, global, multi-center, single arm Phase 1/2 study (BGB-3111-AU-003) of 32 previously treated patients.

For study BGB-3111-206 the efficacy analysis was conducted at a median follow-up of 18,5 months. At the time of analysis, 70 % of patients remained on study. The independent review committee (IRC) assessed overall response rate (ORR) was 83,7 % with a median duration of response (DoR) of 19,5 months. The efficacy analysis was also conducted at a median follow-up of 24,8 months. At time of analysis, 66,3 % of patients remained on study. The investigator assessed ORR was 83,7 % (95% CI: 74,2, 90,8) with a CR rate of 77,9 % and a PR rate of 5,8 %. The median DoR was 24,9 months (95 % CI: 23,1, NE).

For study BGB-3111-AU-003 the efficacy analysis was conducted at a median follow-up of 18,8 months. At time of analysis, 53,1% of patients remained on study. The IRC assessed ORR was 84,4 % with a median DoR of 18,5 months.

The Treatment of Adult Patients With Marginal Zone Lymphoma (MZL)

The efficacy of BRUKINSA was assessed in Study BGB-3111-214, a Phase 2 open-label, multicenter, single-arm trial of 68 previously treated patients with MZL who had received at least one prior anti-CD20-based therapy. Twenty-six (38,2 %) patients had extranodal MZL, 26 (38,2 %) had nodal MZL, 12 (17,6 %) had splenic MZL, and 4 (6 %) patients had unknown subtype.

The efficacy of BRUKINSA was also assessed in BGB-3111-AU-003, an open-label, multicenter, single-arm trial that included 20 patients with previously treated MZL (45 % having extranodal MZL, 25 % nodal, 30 % splenic).

In both studies, MZL patients who received prior treatment with a BTK inhibitor and those with known CNS involvement or transformation to aggressive lymphoma were excluded.

In BGB-3111-214, the median time to response was 2,8 months (range: 1,7 to 11,1 months). The overall response rates were 64 %, 76 %, 67 %, and 50 % for the MZL subtypes (extranodal, nodal, splenic, unknown subtype), respectively.

The Treatment Of Adult Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

The efficacy of BRUKINSA in patients with CLL/SLL was evaluated in two randomised controlled trials.

SEQUOIA (BGB-3111-304)

1.3.1.1 Professional Information

SEQUOIA trial, a randomized global multicenter, open-label, controlled Phase 3 trial of BRUKINSA monotherapy and combination comparator therapy in 479 patients with previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) without the 17p deletion (del(17p)) (Cohort 1). Additional efficacy was evaluated in a SEQUOIA cohort 2, a multicenter single-arm trial of BRUKINSA monotherapy in 110 patients with previously untreated chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) with centrally confirmed del(17p).

Efficacy was based on progression-free survival (PFS) as assessed by independent central review committee (IRC) using the 2008 International Workshop for Chronic Lymphocytic Leukemia (IWCLL) guidelines for CLL and the Lugano criteria for SLL. The median duration of follow-up was 26,2 months (range: 0,0 to 42,2 months). At 24 months, (95 % CI), the event free rate was 85,5 % (80.1, 89.6) for BRUKINSA and 69,5 % (62,4, 75,5) for comparator combination therapy.

In Cohort 2, 110 patients with centrally confirmed del(17p) were enrolled and received BRUKINSA 160 mg twice daily until disease progression or unacceptable toxicity.

The median duration of follow-up for Cohort 2 was 30,5 months (range: 5,0 to 39,1).
At the time of the efficacy results, at 24 months, the progression free survival rate (95 % CI) was 88,9 % (81,3, 93,6) in Cohort 2.

ALPINE (BGB-3111-305)

The efficacy of BRUKINSA in patients with relapsed or refractory CLL/SLL was evaluated in ALPINE, a randomized, global multicenter, open-label, Phase 3, controlled trial. The trial enrolled 652 patients with relapsed or refractory CLL/SLL after at least 1 prior systemic therapy. The patients were randomised in a ratio of 1:1 to either

- BRUKINSA 160 mg orally twice daily until disease progression or unacceptable toxicity, or
- comparator product orally once daily until disease progression or unacceptable toxicity.

The primary efficacy endpoint was overall response rate (ORR; defined as partial response or better) as determined by investigator assessment using the 2008 IWCLL guidelines for CLL and the Lugano criteria for SLL. ALPINE met its primary endpoint of both non-inferiority and superiority for ORR by investigator, as well as ORR by IRC. Efficacy results for ALPINE by independent central review and by investigator were as follows:

For all 652 patients, event-free rates at 12 months for progression-free survival by investigator assessment were 93,3 % (95 % CI, 89,3, 95,9) for the BRUKINSA arm and 83,1 % (95 % CI, 77,3, 87,6) for the comparator arm.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of zanubrutinib were studied in healthy subjects and patients with B-cell malignancies. Zanubrutinib maximum plasma concentration (C_{max}) and area under the plasma drug concentration over time curve (AUC) increase proportionally over a dosage range from 40 mg to 320 mg (0,13 to 1 time the recommended total daily dose). Limited systemic accumulation of zanubrutinib was observed following repeated administration.

The geometric mean (% CV) zanubrutinib steady-state daily AUC is 2 099 (42 %) ng·h/mL following a 160 mg twice daily dose and 1 917 (59 %) ng·h/mL following a 320 mg once daily dose. The geometric mean (%CV) zanubrutinib steady-state C_{max} is 299 (56 %) ng/mL following a 160 mg twice daily dose and 533 (55 %) ng/mL following a 320 mg once daily dose.

Absorption:

The median T_{max} of zanubrutinib is 2 hours.

Food effect: No clinically significant differences in zanubrutinib AUC or C_{max} were observed following administration of a high-fat meal (approximately 1 000 calories with 50 % of total caloric content from fat) in healthy subjects.

Distribution:

The geometric mean (% CV) apparent steady-state volume of distribution of zanubrutinib during the terminal phase (V_z/F) was 522 L (71 %) following a 160 mg twice daily dose. The plasma protein binding of zanubrutinib is approximately 94 % and the blood-to-plasma ratio is 0,7 to 0,8.

Metabolism:

In vitro, zanubrutinib is primarily metabolized by cytochrome P450(CYP)3A.

Elimination: The mean half-life (t½) of zanubrutinib is approximately 2 to 4 hours following a single oral zanubrutinib dose of 160 mg or 320 mg. The geometric mean (% CV) apparent oral clearance (CL/F) of zanubrutinib during the terminal phase was 128 (61 %) L/h. Following a single radiolabeled zanubrutinib dose of 320 mg to healthy subjects, approximately 87 % of the dose was recovered in feces (38 % unchanged) and 8 % in urine (less than 1 % unchanged).

Special Populations and Conditions

Based on population PK analysis, age (19 to 90 years), sex, race (Caucasian, Asian, and others), and body weight (36 to 144 kg) did not have clinically meaningful effects on the PK of zanubrutinib.

Paediatrics:

No pharmacokinetic studies were performed with zanubrutinib in patients under 18 years of age.

Hepatic Insufficiency:

The total AUC of zanubrutinib increased by 11 % in subjects with mild hepatic impairment (Child-Pugh class A), by 21 % in subjects with moderate hepatic impairment (Child-Pugh class B), and by 60 % in subjects with severe hepatic impairment (Child-Pugh class C)

relative to subjects with normal liver function. The unbound AUC of zanubrutinib increased by 23 % in subjects with mild hepatic impairment (Child-Pugh class A), by 43 % in subjects with moderate hepatic impairment (Child-Pugh class B), and by 194 % in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function.

Renal Insufficiency:

Zanubrutinib undergoes minimal renal elimination. Based on population PK analysis, mild and moderate renal impairment (CrCl ≥ 30 mL/min as estimated by Cockcroft-Gault equation) had no influence on the exposure of zanubrutinib. Limited PK data is available in patients with severe renal impairment (CrCl < 30 mL/min) or in patients requiring dialysis.

5.3 Preclinical safety data

General Toxicology

The general toxicologic profiles of zanubrutinib were characterised via oral treatment in Sprague-Dawley rats for up to 6 months and in Beagle dogs for up to 9 months.

In the 6-month study, rats were dosed 30, 100 or 300 mg/kg/day for 182 days, or 1000 mg/kg/day for up to 8 days. The test article related mortality was only noted at the dose of 1000 mg/kg/day following 5-day treatment and the main toxicology findings was gastrointestinal tract toxicity associated with histopathologic changes. Test article related histopathologic changes were noted in pancreas, lung, and skeletal muscle most of which were fully or partially reversible. The NOAEL was considered to be 300 mg/kg/day, where the systemic exposure (AUC) was approximately 25 times in males and 42 times in females of the human exposure at the recommended dose.

In the 9-month study, dogs were dosed 10, 30 or 100 mg/kg/day for 273 days. No mortality occurred throughout the study. The toxicology findings or changes were minimal or mild and resolved during recovery phase, including abnormal stool, conjunctiva hyperemia, lymphoid depletion or erythrophagocytosis in the gut-associated lymphoid tissues. The NOAEL was

considered to be 100 mg/kg/day, where the systemic exposure (AUC) was approximately 20 times in males and 18 times in females of the human exposure at the recommended dose.

Carcinogenicity

Carcinogenicity studies have not been conducted with zanubrutinib.

Genotoxicity

Zanubrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in rats.

Developmental and Reproductive Toxicity

A combined male and female fertility and early embryonic development study was conducted in rats at oral zanubrutinib doses of 30 to 300 mg/kg/day. Male rats were dosed 4 weeks prior to mating and through mating and female rats were dosed 2 weeks prior to mating and to gestation day 7. No effect on male or female fertility was noted but at the high dose of 300 mg/kg day, morphological abnormalities in sperm and increased post-implantation loss were noted. The high dose of 300 mg/kg/day is approximately 9 times the human recommended dose, based on body surface area.

Embryo-fetal development toxicity studies were conducted in both rats and rabbits.

Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2- or 3-chambered hearts) were noted at all dose levels (incidence between 0.3% and 1.5%) in the absence of maternal toxicity. The lowest dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose.

Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 33 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre- and post-natal developmental toxicity study in rats, zanubrutinib was administered orally at 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from

the 75 mg/kg/day and 150 mg/kg/day groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g. cataract, protruding eye). The dose of 30 mg/kg/day is approximately 4 times the AUC in patients receiving the recommended dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ammonium hydroxide (trace), colloidal silicon dioxide, croscarmellose sodium, dehydrated ethanol (trace), gelatin, iron oxide black (trace), isopropyl alcohol (trace), magnesium stearate, microcrystalline cellulose, n-butyl alcohol (trace), propylene glycol (trace), purified water (trace), shellac glaze in ethanol (trace), sodium lauryl sulphate, titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

120 capsules are packed in a 200 mL white HDPE round bottle with a child-resistant screw cap with a printed heat sealable foil laminate liner.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

BeiGene South Africa (Pty) Ltd.

VilleBois Office Park

920 De Ville Bois Mareuil Drive

Moreleta Park X36

Pretoria 0044

South Africa

8 REGISTRATION NUMBER(S)

58/26/0130

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF TEXT

30 January 2024